

27. (Amended) An MRI agent according to claim 12, 13, or 14 wherein said polymer comprises a plurality of said MRI agents.

28. (Amended) A method of magnetic resonance imaging of a cell, tissue or patient comprising administering an MRI agent according to claim 12, 13, or 14 to a cell, tissue or patient and rendering a magnetic resonance image of said cell, tissue or patient.

Please add the following new claims:

--29. (New) An MRI agent according to claim 12, 13, or 14 wherein

~~~~~ is a dextran polymer;

M is a DOTA chelator comprising a Gd(III) paramagnetic metal ion;

R<sub>26</sub> and R<sub>27</sub> are alkyl linker groups;

R<sub>28</sub> is a peptide blocking moiety; and,

n is an integer.--

#### REMARKS

Claims 12-23, and 25-29 are pending. Claim 24 has been cancelled without prejudice or disclaimer as drawn to a non-elected invention. Cancellation of claim 24 does not affect inventorship. Claims 13 and 14 have been amended to depend from claim 12 and to clarify that ~~~~~ represents a polymer. Claim 15 has been amended to depend from claims 12, 13 and 14 and to fix a typographical error, i.e., FE to Fe. Claims 17, 19, 21, and 22 have been amended to depend from claims 12, 13 and 14. Claim 23 has been amended to correct a typographical error, i.e., "an" to "a". Claim 25 has been amended to depend from claims 12, 13, and 14 and to clarify that polymers may be polyanionic polymers, polycationic polymers and mixtures of polymers. Support for this amendment is found in the

specification at page 33, lines 18-30. Claim 29 is newly added. Support for newly added Claim 29 is found in the specification at page 12, lines 3-4 (DOTA/Gd(III) complex); page 18, lines 19-25 (peptide blocking moiety); page 23, lines 6-26 (alkyl linking groups); and page 33, line 20. An Appendix of Pending Claims is attached for the Examiner's convenience.

## **RESTRICTION REQUIREMENT**

In response to the Restriction Requirement, Applicants elect for further prosecution the claims of Group VI, namely Claims 12-21, 22, 23 and 25-28, drawn to a composition and use thereof comprising a polymer, a chelator, a linking group, and a blocking moiety other than those of Groups I-V. **This election is made with traverse.**

## **TRAVERSAL OF RESTRICTION REQUIREMENT**

Applicants respectfully submit that the Examiner has mischaracterized what is essentially an election of species as a restriction requirement. Specifically, Applicants note that Claims 12-28 have been restricted into six groups on the basis of the blocking moiety: PELR (Group I, claims 12-28), PLGLAR (Group II, claims 12-28); PGLWA-D-ARG (Group III, claims 12-28); PMALWMR (Group IV, claims 12-28); PMGLRA (Group V, claims 12-28); and a blocking moiety other than those of Groups I-V (Group VI, claims 12-23 and 25-28).

If a patent application claims two or more independent and distinct inventions, the application may be restricted to one invention (USC § 121). The term "independent" is interpreted to mean that there is no disclosed relationship between the two or more subjects disclosed. The term "distinct" is interpreted to mean that two or more inventions are (1) capable of separate manufacture, use or sale as claimed, and (2) patentable over each other

(M.P.E.P. § 802.01). However, in practice, a restriction of claims may be required in a single application for related, dependent inventions that are distinct if (1) each distinct invention has a separate classification in the Patent Office patent classification system, (2) each distinct invention has a separate status in the art, or (3) a different field of search is necessary for each distinct invention (M.P.E.P. § 802.02).


Applicants submit that the restriction requirement in the present application is inappropriate for the following reasons. First, restricted Groups I-VI are classified in the same class (424) and subclass (9.3). Thus, each invention does not have a separate classification in the Patent Office patent classification system.

Second, the Examiner has not provided an explanation as to why each invention has attained recognition in the art as a separate subject for inventive effort or as to why it is necessary to search for one of the inventions in places where no pertinent art to the other inventions exist. As the only difference between restricted Groups I-IV is the nature of the blocking moiety, Applicants submit that it is not necessary to search for one of the inventions in places where no pertinent art to the one or more of the other inventions exist. Accordingly, Applicants respectfully submit that this restriction requirement is improper and request it be withdrawn.

Alternatively, if the Examiner does not withdraw the restriction requirement, Applicants provisionally elect with traverse the claims of Group VI, namely Claims 12-21, 22, 23 and 25-28, drawn to a composition and use thereof comprising a polymer, a chelator, a linking group, and a blocking moiety other than those of Groups I-V.

## **SPECIES ELECTION REQUIREMENT**

The applicant is further required to elect a species and identify the claims readable on the elected species. The applicants hereby provisionally elect the species claimed in new claim 29, comprising a dextran polymer, DOTA complexed with Gd(III), alkyl linking groups and a peptide blocking moiety. Applicants note that this structure corresponds in claim 12 as amended to:

 is a dextran polymer;

M is Gd(III);

R<sub>26</sub> and R<sub>27</sub> are alkyl groups;

R<sub>28</sub> is a peptide; and

n is an integer.

Claims 12-23 and 25-28 read on the species elected. **This election is made with traverse.**

#### **TRAVERSAL OF SPECIES ELECTION REQUIREMENT**

Applicants submit that the blocking moieties of the claimed MRI agents should not be subjected to an election of species requirement. If the search and examination of an entire application can be made without serious burden, it must be examined on its merits even though it includes claims to independent or distinct inventions. (MPEP § 803).

The MRI agents of the present invention comprise a polymer, a chelator, a paramagnetic ion, linking groups and a blocking moiety. The blocking moiety is chosen such that it interacts with a target substance resulting in an MRI image if the target substance is present. Thus, the invention is directed to activatable MRI agents used to detect a target substance in a cell or tissue. Therefore, further prosecution without an election would not burden the Examiner. Accordingly, Applicants respectfully submit that this election requirement is improper and request it be withdrawn.

Alternatively, if the Examiner does not withdraw the species election requirement, Applicants provisionally elect with traverse the species claimed in new claim 29, i.e., the species comprising a dextran polymer, DOTA complexed with Gd(III), alkyl linking groups and a peptide blocking moiety.

Applicants make this election with the understanding that should allowable subject matter be found, applicants are entitled to consideration of a generic claim encompassing additional species, such as those disclosed in claims 12-23 and 25-28.

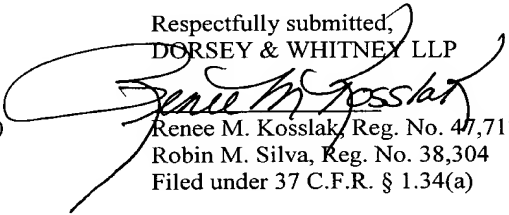
Attached hereto is a marked-up version of the changes made to the specification by the current amendments. The attached page is captioned "Version with markings to show changes made."

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Dated: 10/25/02

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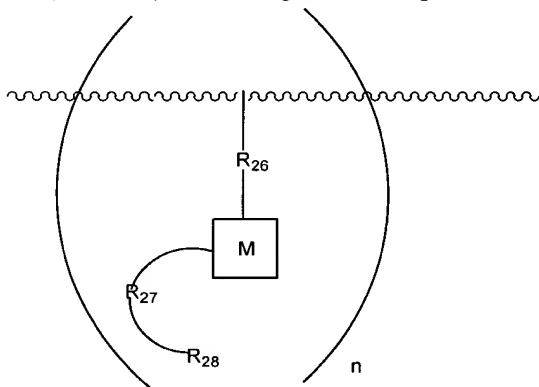
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Filed under 37 C.F.R. § 1.34(a)

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In the Claims**

Claim 13 has been amended as follows

13. (Amended) An MRI agent according to claim 12 having the formula comprising:



wherein

wavy line is a polymer;

M is a chelator comprising a paramagnetic metal ion;

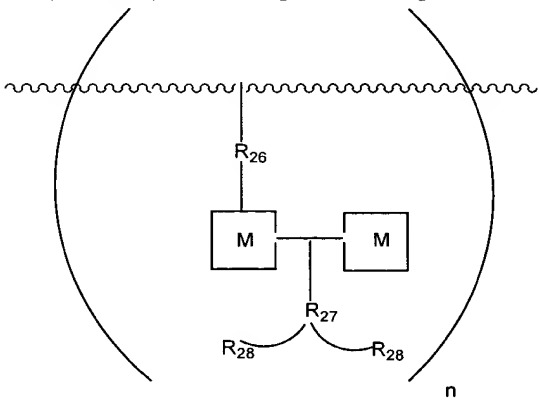
R<sub>26</sub> and R<sub>27</sub> are linker groups;

R<sub>28</sub> is a blocking moiety; and,

n is an integer.

Claim 14 has been amended as follows:

14. (Amended) An MRI agent according to claim 12 having the formula comprising:



wherein

~~~~~ is a polymer;

M is a chelator comprising a paramagnetic metal ion;

R<sub>26</sub> and R<sub>27</sub> are linker groups;

R<sub>28</sub> is a blocking moiety; and

n is an integer.

Claim 15 has been amended as follows:

15. (Amended) An MRI agent according to claims 12, [2]13, or [3]14 wherein said paramagnetic metal ion is selected from the group comprising gadolinium III (Gd+3 or Gd(III)), iron III (Fe+3 or F[Fe](III)), manganese II (Mn+2 or Mn(II)), dysprosium (Dy+3 or Dy(III)), or chromium (Cr+3 or Cr(III)).

Claim 17 has been amended as follows

17. (Amended) An MRI agent according to claims 12, [2]13, or [3]14 wherein said linker groups are alkyl groups.

Claim 19 has been amended as follows:

19. (Amended) An MRI agent according to claims 12, [2]13, or [3]14 wherein said linker groups are aryl groups.

Claim 21 has been amended as follows:

21. (Amended) An MRI agent according to claims 12, [2]13, or [3]14 wherein at least one of said linker groups are selected from the group comprising p-aminobenzyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, propionic acid, aminobutyl, p-alkyl phenols, and 4-alkylimidazole.

Claim 22 has been amended as follows:

22. (Amended) An MRI agent according to claims 12, [2]13, or [3]14 wherein said blocking moiety is a peptide.

Claim 23 has been amended as follows:

23. (Amended) An MRI agent according to claim 22 wherein said peptide binds to a[n] metalloproteinase.

Claim 25 has been amended as follows:

25. (Amended) An MRI agent according to claims 12, [2]13, or [3]14 wherein said polymer is selected from the group comprising functionalized dextrans, styrene polymers, polyethylene, [polyanions and polycations] polyanionic polymers, polycationic polymers, and mixed polymers.

Claim 27 has been amended as follows:

27. (Amended) An MRI agent according to claim 12, [2]13, or [3]14 wherein said polymer comprises a plurality of said MRI agents.

Claim 28 has been amended as follows:

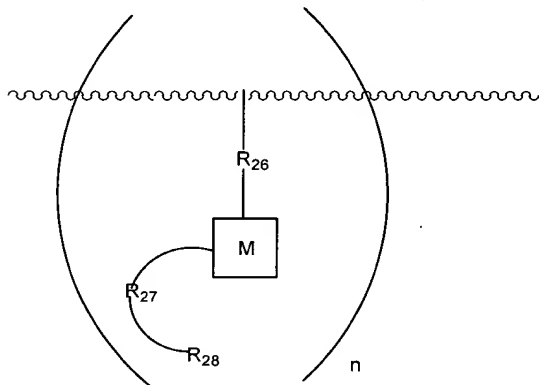
28. (Amended) A method of magnetic resonance imaging of a cell, tissue or patient comprising administering an MRI agent according to claim 12, [2]13, or [3]14 to a cell, tissue or patient and rendering a magnetic resonance image of said cell, tissue or patient.

## APPENDIX OF PENDING CLAIMS

12. A composition comprising:

- a) a polymer;
- b) at least one MRI agent comprising:
  - i) at least one chelator comprising a paramagnetic metal ion; and,
  - ii) a blocking moiety covalently attached to said chelator which hinders the rapid exchange of water in the remaining coordination sites, wherein said blocking moiety will interact with a target substance such that the exchange of water in the remaining coordination sites is increased; and
- c) a linker group attaching said MRI agent to said polymer.

13. (Amended) An MRI agent according to claim 12 having the formula comprising:



wherein

~~~~~ is a polymer

M is a chelator comprising a paramagnetic metal ion;

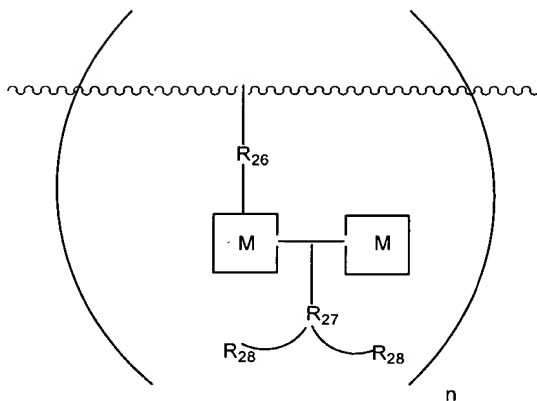
R<sub>26</sub> and R<sub>27</sub> are linker groups;

R<sub>28</sub> is a blocking moiety; and,

n is an integer.

14. (Amended) An MRI agent according to claim 12 having the formula comprising:





wherein

~~~~~ is a polymer;

M is a chelator comprising a paramagnetic metal ion;

R<sub>26</sub> and R<sub>27</sub> are linker groups;

R<sub>28</sub> is a blocking moiety; and

n is an integer.

15. (Amended) An MRI agent according to claims 12, 13, or 14 wherein said paramagnetic metal ion is selected from the group comprising gadolinium III (Gd<sup>+3</sup> or Gd(III)), iron III (Fe<sup>+3</sup> or Fe(III)), manganese II (Mn<sup>+2</sup> or Mn(II)), dysprosium (Dy<sup>+3</sup> or Dy(III)), or chromium (Cr<sup>+3</sup> or Cr(III)).

16. An MRI agent according to claim 15 where said paramagnetic ion is Gd(III).

17. (Amended) An MRI agent according to claims 12, 13 or 14 wherein said linker groups are alkyl groups.

18. An MRI agent according to claim 17 wherein said alkyl groups are substituted alkyl groups.

19. (Amended) An MRI agent according to claims 12, 13 or 14 wherein said linker groups are aryl groups.

20. An MRI agent according to claims 19 wherein said aryl groups are substituted aryl groups.

21. (Amended) An MRI agent according to claims 12, 13 or 14 wherein at least one of said linker groups are selected from the group comprising p-aminobenzyl, methyl, ethyl, propyl, butyl, pentyl, hexyl, propionic acid, aminobutyl, p-alkyl phenols, and 4-alkylimidazole.

22. (Amended) An MRI agent according to claims 12, 13 or 14 wherein said blocking moiety is a peptide.

23. (Amended) An MRI agent according to claim 22 wherein said peptide binds to a metalloproteinase.

25. (Amended) An MRI agent according to claims 12, [2]13, or [3]14 wherein said polymer is selected from the group comprising functionalized dextrans, styrene polymers, polyethylene, polyanionic polymers, polycationic polymers, and mixed polymers.

26. An MRI agent according to claim 25 wherein said polycation is polylysine.

27. (Amended) An MRI agent according to claim 12, 13, or 14 wherein said polymer comprises a plurality of said MRI agents.

28. (Amended) A method of magnetic resonance imaging of a cell, tissue or patient comprising administering an MRI agent according to claim 12, 13, or 14 to a cell, tissue or patient and rendering a magnetic resonance image of said cell, tissue or patient.

29. (New)